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Challenges in prenatal screening and diagnosis in the Netherlands

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Targeted ultrasound examination and DNA testing for Noonan syndrome, in fetuses with increased nuchal translucency and normal karyotype

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Targeted ultrasound examination and DNA testing for Noonan syndrome, in fetuses with increased nuchal translucency and normal karyotype

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Objective:

To define sonographic criteria that may improve the prenatal diagnosis of Noonan syndrome by targeted DNA testing.

Methods:

We searched our Fetal Medicine Unit records for all cases with a final diagnosis of Noonan syndrome. A literature review was undertaken to identify the sonographic features of Noonan syndrome fetuses. Information was pooled to define the most common features.

Results:

In our database, we identified three cases of Noonan syndrome. The diagnosis was suspected prenatally in two of them. Thirty-nine cases were identified

in the literature. In the presented cases we show that suspicion of Noonan syndrome should arise when, after an increased nuchal translucency, ultrasound investigation in the second trimester shows a persistent nuchal fold (NF) or cystic hygroma in combination with at least one of the following features: hydrops fetalis, pleural effusion, cardiac anomalies, polyhydramnios or specific facial abnormalities.

Conclusion:

Prenatal ultrasound findings in Noonan syndrome can be subtle and aspecific, but when specific characteristics are present additional targeted DNA analysis is indicated.

Introduction

Measurement of the nuchal translucency (NT) at 11-13 weeks 6 days of gestation is an established screening method for fetal aneuploidy (Snijders et al., 1998). Chromosomally normal fetuses with an increased NT (above the 95th centile for gestational age) are at increased risk of adverse pregnancy outcome. Moreover, an increased NT thickness has also been associated with a wide range of structural abnormalities and genetic syndromes involving neurodevelopmental delay (Pajkrt et al., 1999; Souka et al., 2005; Bilardo et al., 2007; Senat et al., 2007). Among the genetic syndromes the most frequently

reported is Noonan syndrome.

Noonan syndrome is an autosomal dominant disorder with a prevalence between 1 : 1000 and 1 : 2500 live births (Nora et al., 1974; Allanson, 1993). The majority of postnatal diagnosis concern *de novo* mutations; however, an affected parent is found in 30-75% of families (Van Huizen et al., 2005). Diagnosis of Noonan syndrome is often challenging because of the great variability in clinical characteristics (Allanson, 1993; Noonan, 1994). The main facial characteristics are hypertelorism, downslanting palpebral fissures, epicanthic fold, ptosis and low set posteriorly angulated ears. The most common cardiovascular defects are pulmonary valve stenosis and hypertrophic cardiomyopathy (HCM). Other phenotypic characteristics are short stature, broad or webbed neck and chest deformity. Associated pathologies are hematological disorders (bleeding diathesis, juvenile myelomonocytic leukemia), lymphatic vessel dysplasias, deafness and cryptorchidism. Affected individuals show a wide range in level of intelligence, with mental retardation being present in 15-35%, usually in the mild range and mainly consisting of specific visual-constructional problems and verbal performance discrepancy (Sharland et al., 1992; Allanson, 1993; Van der Burgt et al., 1999; Van der Burgt, 2007).

Besides the variability in expression, the facial phenotype changes with age resulting in less pronounced features in adults (Allanson, 1993). At present a simple and accurate scoring system, proposed by Van der Burgt et al. in 1994, is used for the (postnatal) diagnosis of Noonan syndrome (Van der Burgt, 2007).

Here we report our experience with ultrasound findings in three cases of Noonan syndrome, two of which were diagnosed prenatally, following ultrasonographic evaluation of an increased NT and normal karyotype. These data, together with a detailed review of the published literature will serve as a useful aid to facilitate targeted DNA testing and parental counseling. A special focus is set on the role that 3D ultrasound may play in the diagnostic work-up of these pregnancies.

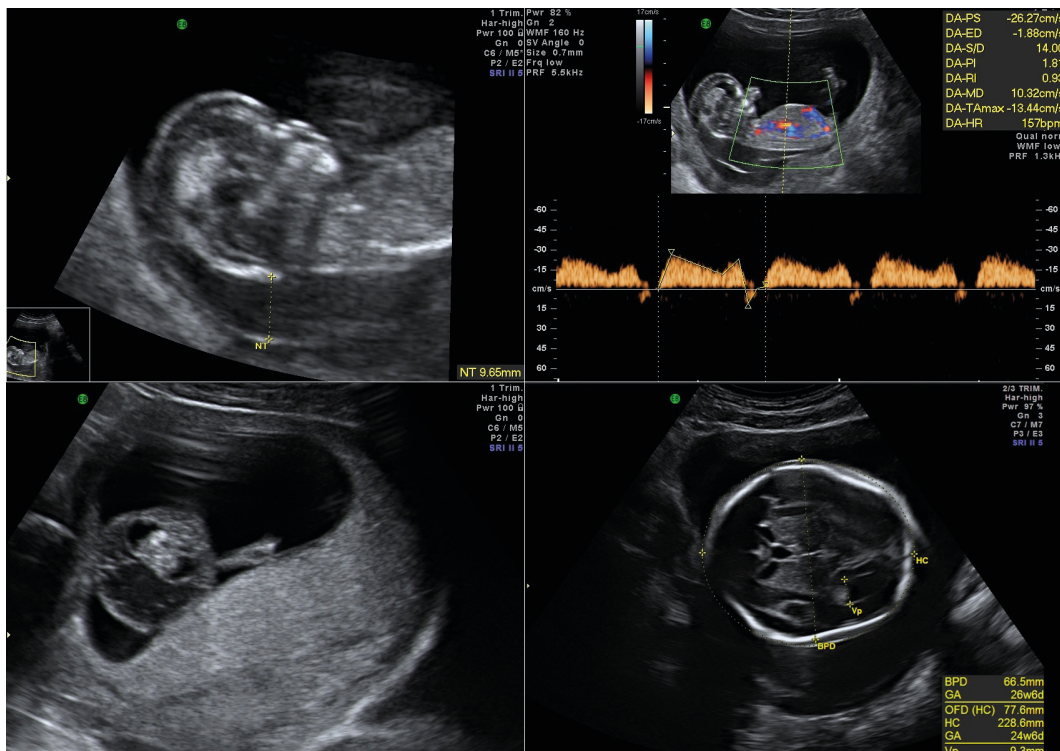
Results

CASE 1

A 24-year-old primigravida was referred to our Fetal Medicine Unit (FMU) because of an increased NT of 9.6 mm at 12+6 weeks of gestation (Figure 1a). Detailed first trimester US examination revealed a hypoplastic nasal bone. Brachycephaly, generalized edema and a ventricular septal defect were suspected. Ductus venosus flow showed a reversed a-wave and a pulsatility index for veins (PIV) of 4.00 (Figure 1b). Moreover, low resistance and high velocity hepatic artery flow were observed. No other structural anomalies were detected. Due to the increased risk of aneuploidy, chorionic villus sampling (CVS) was performed and demonstrated a normal male karyotype (Table 1).

The ultrasound scan was repeated at 14+4 weeks of gestation. The NT was still 6.8 mm and bilateral distended jugular lymphatic sacs (JLS) were noted (Figure 1c).

Follow-up sonography at 20+5 weeks of gestation showed a nuchal skin fold of 8 mm, bilateral distended JLS and brachycephaly (Figures 1d and 2a). Fetal echocardiography showed a structural and functional normal heart. The rest of the fetal biometry was nor-



■ Figure 1 – (a) First trimester sagittal view of case 1 showing an increased nuchal translucency. (b) Ductus Venos Doppler measured in the first trimester showing a reversed a-wave. (c) First trimester transverse view showing the increased nuchal translucency and distended lymphatic jugular sacs. (d) Second trimester transverse view of the skull showing a brachycephaly.

mal and no other structural anomalies were detected.

At 23 weeks 4 days of gestation three-dimensional (3D) ultrasound of the fetus showed facial features typical for Noonan syndrome (hypertelorism, low set ears, broad nose and lips) and the parents were counseled about the possibility of Noonan syndrome (Figure 2b and c).

The patient continued prenatal care in her local hospital, only to be referred back at 36 weeks 3 days with severe bilateral hydrothorax, mild generalized edema and polyhydramnios (AFI 31.4 cm). The pulsatility index (PI) of the umbilical artery was increased and there was redistribution in the middle cerebral artery (MCA). The next day all Doppler parameters deteriorated and labor was induced. A boy weighing 3000 g was born by caesarean section, performed for fetal distress, with Apgar scores of 4 and 5 at 1 and 5 min, respectively, and an umbilical artery pH of 7.14 with a base excess (BE) of -8. The baby presented with the following dysmorphic features: downward palpebral slant, epicanthus, telecanthus, low set posteriorly angulated ears, low posterior hairline, broad nose, increased distance between the nipples, tendency to clinodactyly, less pronounced palmar grooves and cryptorchidism. Echocardiography showed poly-valvular disease ('nodular compaction of the aortic and pulmonary valve, long chorda tendinae of the mi-

tral valve, tricuspid valve insufficiency and bidirectional shunt over the ductus arteriosus, good left ventricular function and mild hypertrophy). A chest X-ray confirmed a chylothorax with a right-sided pneumothorax. Newborn hearing screening was sufficient on the left, but insufficient on the right.

■ Table 1 – Prenatal and postnatal findings in the three Noonan syndrome cases

Prenatal and postnatal findings in Noonan syndrome	Case 1	Case 2	Case 3
Age of the mother (years)	24	28	33
Primigravida/multigravida	Primigravida	Primigravida	Primigravida
<i>Prenatal findings:</i>			
Increased NT (mm)	9.6	4.4	6.0
Distended JLS	Yes, still present at 23+4 weeks	No	Yes
Ductus venosus	Reversed a-wave	Not performed	Reversed a-wave
Hepatic artery	Low resistance flow	Not performed	Low resistance flow
Nasal bone	Hypoplastic	Hypoplastic	Normal
Increased NF second trimester	Yes	Yes	No
Edema	At 36 weeks 3 days; severe bilateral hydrothorax and mild generalized edema	TOP	No
Facial features	Hypertelorism, low set ears, broad nose and lips, brachycephaly	Low set ears with uplifted earlobes, small nose, sloping forehead, brachycephaly	Unknown
Cardiac anomalies	No	Malalignment VSD, deviation of the heart axis, mild TR, right ventricular dysfunction, pericardial effusion	Suspicion of a small VSD
Renal anomalies	No	Bilateral pyelectasis	No
Amniotic fluid	At 36 weeks 3 days; polyhydramnios	Normal	At 27 weeks 5 days; polyhydramnios
Short femur	No	No	No
Other anomalies	No	Mild ventriculomegaly	No
<i>Postnatal findings:</i>			
Dysmorphic facial features	Downward palpebral slant, epicanthus, telecanthus, low set posteriorly angulated ears, broad nose, low posterior hairline	Low set posteriorly angulated ears, road nose, brachycephaly	Downward palpebral slant, telecanthus, low set ears
Other dysmorphic features	Increased distance between the nipples, tendency to clinodactyly, reduced palmar grooves,	Redundant nuchal skin, muscular physique	Short stature, pectus carinatum, asymmetrical thorax
Cardiac anomalies	Poly-valvular disease	Left ventricular hypertrophy, subaortic stenosis, perimembranous VSD	No
Edema	Chylothorax	Generalized skin edema	No
DNA mutation	PTPN11 (c.124A>G (p.Thr42Ala)), <i>de novo</i>	RAF1 (c.770C>T (p.Ser257Leu)), <i>de novo</i>	PTPN11 (c.417G>C, p.Glu139Asp), <i>de novo</i>

NT = nuchal translucency. JLS = jugular lymphatic sacs. VSD = ventricular septal defect. TR = tricuspid regurgitation.



■ Figure 2 – (a) Second trimester transverse view of the skull showing a brachycephaly. (b) Three-dimensional (3D) view of fetal face showing hypertelorism, broad nose and thick lips. (c) 3D view of fetal face showing hypertelorism, broad nose and thick lips.

As both prenatal and postnatal findings were suggestive of Noonan syndrome, DNA testing was performed and showed a PTPN11 mutation (c.124A>G (p.Thr42Ala)), confirming the diagnosis. Both parents are not carriers of the mutation.

Two weeks after birth a bone marrow biopsy was performed in view of a monocytosis, leukocytosis and hepatomegaly. An acute monocytic reaction, suspicious for juvenile monocytic myelogenous leukemia (JMML), was diagnosed. As a germ-line mutation on exon 2 was found, the diagnosis of JMML was unlikely (differential diagnosis transient leukaemoid reaction). The baby received a low dosed Cytarabine (ARA-C) treatment for 5 days and was doing well after treatment.

CASE 2

A 28-year-old primigravida was referred to our FMU because of an increased NT of 4.4 mm at 11 weeks 4 days of gestation. A hypoplastic nasal bone and a cyst in the posterior fossa were also observed. No other structural anomalies were detected. Due to the increased risk of aneuploidy, CVS was performed and demonstrated a normal female karyotype.

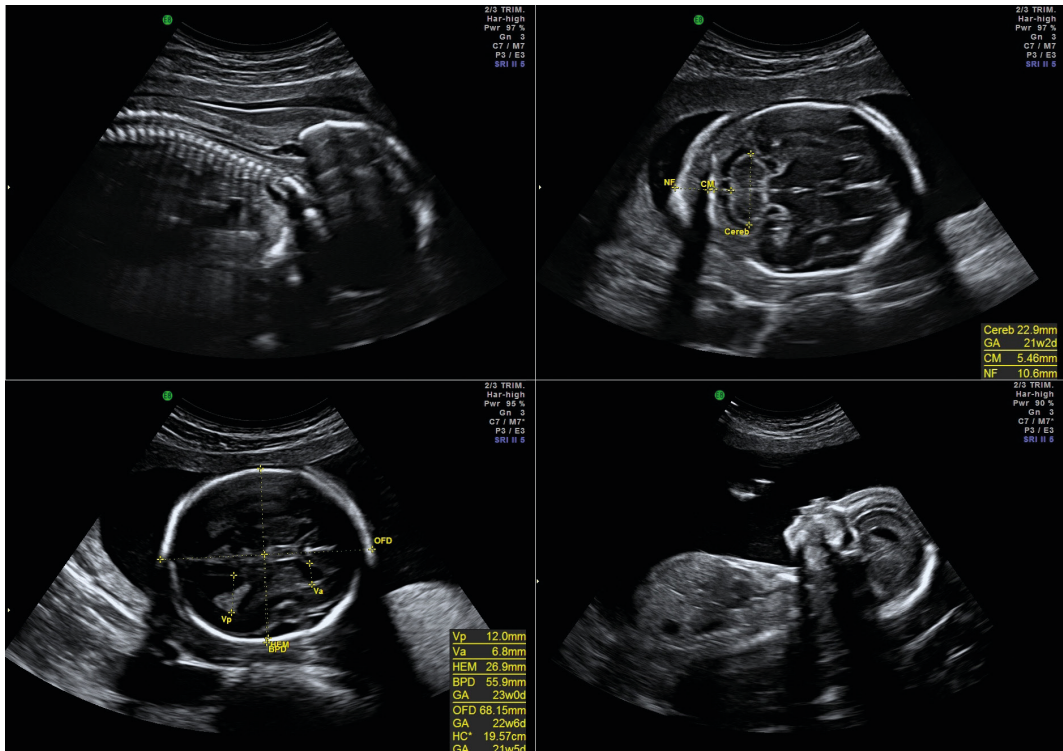
An ultrasound examination at 15 weeks in her local hospital reported no structural

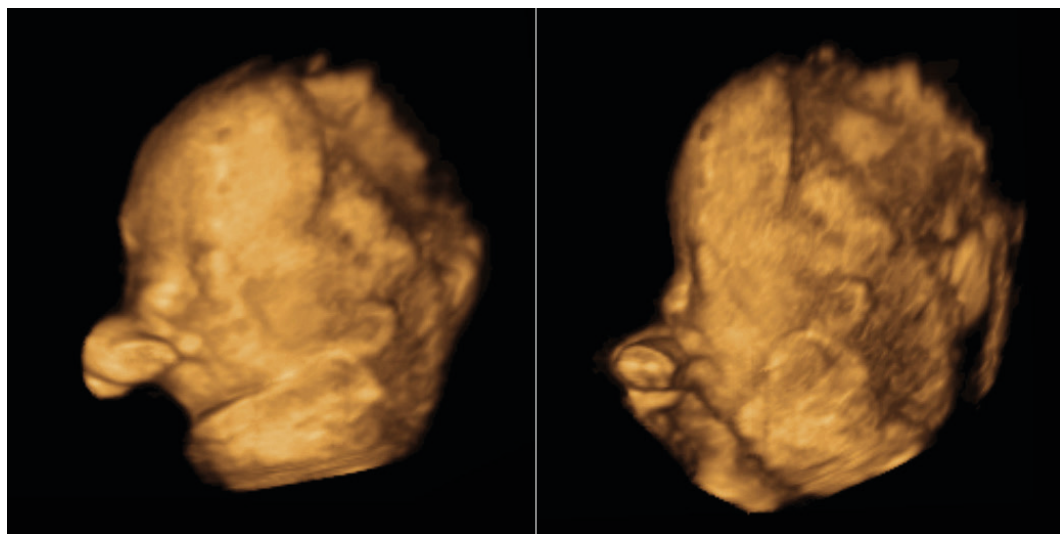
anomalies, besides mild cardiac disproportion and because of this finding the patient was referred back to us for the 20-week scan. Follow-up sonography at 19+5 weeks of gestation showed a nuchal skin fold of 7.7 mm (Figure 3a and b), wide anterior and normal posterior horns (9.6 and 8.8 mm), small nose, sloping forehead, brachycephaly (Figure 3c and d) and bilateral pyelectasis. Fetal echocardiography showed a heart axis deviated to the left, mild pericardial effusion, a small subaortic malalignment ventricular septal defect (VSD), moderate tricuspid regurgitation and right ventricular dysfunction. Fetal biometry was normal and no other structural anomalies were detected (Table 1).

At 20 weeks 3 days of gestation an MRI was performed showing normal intracranial structures, normal gyri and mild ventriculomegaly. Follow-up at 21 weeks 3 days of gestation demonstrated a nuchal skin fold of 10.6 mm and low set ears with uplifted earlobes (Figure 4a and b).

As above-mentioned findings were suggestive of Noonan or Costello syndrome, the parents were counseled as such. They decided to terminate the pregnancy. A female baby of 590 g was born at 22 weeks 1 day of gestation. Examination by the clinical geneticist confirmed the classical facial features and muscular physique suggestive of Noonan syndrome. Autopsy ascertained the presence of low set ears, generalized skin edema, redun-

■ Figure 3 – (a) Second trimester sagittal view showing an increased nuchal fold. (b) Second trimester transverse view of the skull, showing the increased nuchal fold. (c) Second trimester transverse view of the skull, showing a brachycephaly. (d) Second trimester sagittal view showing the profile of the fetus with a thickened prenasal thickness.





■ Figure 4 – (a) Three-dimensional (3D) view of fetal face showing the low set ears. (b) 3D view of fetal face showing the thick lips and low set ears.

dant nuchal skin, left ventricular hypertrophy, subaortal stenosis and a perimembranous VSD. Placenta pathology was normal and X-ray showed no abnormalities.

DNA analysis showed a *RAF1* mutation (c.770C>T(p.Ser257Leu)) making a definitive diagnosis of Noonan syndrome. Both parents are not carriers of this mutation.

CASE 3

A 33-year-old primigravida was referred to our FMU because of an increased NT of 6.0 mm at 12 weeks 4 days of gestation. No other structural anomalies were detected. Ductus venosus showed a reversed a-wave and the PIV was 3.40. Due to the increased risk of aneuploidy, CVS was performed demonstrating a normal female karyotype.

Ultrasound scanning was repeated at 14+4 weeks' gestation. Although the NT was almost normalized, bilateral distended JLS were observed. The PIV of the ductus venosus was increased (1,32), but with a positive a-wave (Table 1).

Follow-up sonography at 20 weeks 6 days of gestation showed no structural abnormalities and normal fetal biometry. Fetal echocardiography showed a structural and functional normal heart.

At 27 weeks 5 days, 29 weeks 6 days, 32 weeks 6 days, 36 weeks 6 days of gestation sonography demonstrated a progressive polyhydramnios (AFI 33.0-37.1). Normal stomach- and bladder-filling were present. Besides the suspicion of a small VSD, no other abnormalities were seen.

At 39 weeks 3 days of gestation, after an uncomplicated vaginal delivery, a girl of 3350 g was delivered. Apgar scores were 8 and 10 at 1 and 5 min, respectively.

At 19 months of age, because of dysmorphic features (short stature (-2SD), telecanthus, downward palpebral slant, low set ears, pectus carinatum, asymmetrical thorax,

increased distance between the nipples) and possible motor delay were suggestive of Noonan syndrome, DNA testing was performed, which showed a PTPN11 mutation (c.417G>C, p.Glu139Asp). Both parents are not carriers of this mutation.

Discussion

In this report we have demonstrated that the diagnosis of Noonan syndrome can be made prenatally when the pattern of anomalies is recognized, especially in case of subtle dysmorphic features in fetuses after increased NT and normal karyotype. Three-dimensional investigation may be helpful in defining the diagnosis and attention should be focused on the nose, mouth, ears and profile of the fetus. Diagnosis of Noonan syndrome is important as the prognosis for individuals may vary.

In a previous study we reported that one out of five chromosomally normal fetuses with increased NT has an adverse pregnancy outcome (Bilardo et al., 2007). As genetic syndromes are diagnosed in around 5% of the fetuses, additional investigations should be considered (Bilardo et al., 2007). Noonan syndrome is the most frequently reported genetic syndrome in association with an increased NT, with a prenatal incidence ranging between 1 and 3% (Brady et al., 1998; Souka et al., 1998; Hiippala et al., 2001).

Approximately 50% of Noonan syndrome cases are caused by missense mutations in the PTPN11 gene on chromosome 12 (Tartaglia et al., 2001). PTPN11 encodes the non-receptor protein tyrosine phosphatase SHP-2. The mutations associated with Noonan syndrome result in a gain of function of SHP-2. This protein participates in a wide variety of intracellular signal cascades elicited by a number of growth factors, cytokines and hormones, and is required in several developmental processes (Tartaglia et al., 2001, 2002). Mutations in the SOS1-, RAF1-, KRAS-, BRAF-, MAP2K1/2-, NRAS- and SHOC2-gene have been described to account for a small percentage of Noonan syndrome cases (Jorge et al., 2009). The above-mentioned genes, especially mutations in the RAS/MAPK pathway, are not only involved in the pathogenesis of Noonan syndrome but also in four syndromes with clinical features overlapping with Noonan syndrome; Leopard syndrome, Cardiofacio-cutaneous syndrome, Costello syndrome and Neurofibromatosis type 1 (Schubbert et al., 2007).

In the presented cases we show that suspicion of Noonan syndrome should arise when, after an increased NT, ultrasound investigation in the second trimester shows a persistent NF or cystic hygroma in combination with at least one of the following features: hydrops fetalis, pleural effusion, cardiac anomalies, polyhydramnios or specific facial abnormalities (Table 1) (Witt et al., 1987; Benacerraf et al., 1989; Izquierdo et al., 1990; Sonesson et al., 1992; Nisbet et al., 1999; Achiron et al., 2000; Bradley et al., 2001; Menashe et al., 2002; Witters et al., 2002; Eccles et al., 2003; Gandhi et al., 2004; Ragavan et al., 2005; Schluter et al., 2005; Becker et al., 2007; Bekker et al., 2007; Kiyota et al., 2008; Gonzalez-Huerta et al., 2010; Houweling et al., 2010).

Heart anomalies are found in 60-70% of the postnatal cases (mostly pulmonary stenosis, ASDs and hypertrophic obstructive cardiomyopathy) and will be one of the major causes requiring medical attention (Sharland et al., 1992; Allanson, 1993). HCM is present in 10-20% of the cases and the clinical course varies from asymptomatic to rapidly progressive heart failure in infancy (Allanson, 1987; Van der Burgt, 2007). Above-men-

tioned cardiac anomalies are often missed prenatally as they are typical examples of late onset malformations which may appear during the third trimester of pregnancy or even after birth (Achiron et al., 2000; Menashe et al., 2002), this should be discussed with the parents. In our series and in the literature a CHD was diagnosed prenatally in 16 of the 42 Noonan syndrome cases (38.1%), which is significantly lower than diagnosed postnatally in Noonan syndrome infants.

As above-mentioned findings are mild and not specific, being common to other syndromes and sometimes also present in normal fetuses it is necessary to define which sonographic findings should prompt targeted prenatal DNA diagnostics for Noonan syndrome (Nisbet et al., 1999; Schluter et al., 2005).

Houweling et al. (2010) advocate that given the high incidence of Noonan syndrome in fetuses with increased NT and normal karyotype, genetic counseling and Noonan syndrome mutation detection should always be offered, even in the absence of additional

■ Table 2 – Prenatal findings in Noonan syndrome in the literature^a

Prenatal findings in Noonan syndrome	Our cases		Literature		Total	
	N	%	N	%	N	%
Total cases	3	100	39	100	42	100
Increased NT/cystic Hygroma	3	100	12	30.8	15	35.7
Distended JLS	2	66.7	5	12.8	7	16.7
Increased NF/cystic hygroma second trimester	2	66.7	19	48.7	21	50
<i>Edema:</i>						
Pleural effusion	1	33.3	16	41	17	40.5
Ascites	0	0	6	15.4	6	14.3
Scalp/skin edema	1	33.3	13	33.3	14	33
<i>Facial features:</i>						
Brachycephaly	2	66.7	1	2.6	3	7.1
Hypertelorism	2	66.7	0	0	2	4.8
Low set ears	2	66.7	5	12.8	7	16.7
Broad nose	1	33.3	3	7.7	4	9.5
Full lips	1	33.3	3	7.7	4	9.5
Cardiac anomalies ^b	1	33.3	15	38.5	16	38.1
Renal anomalies ^c	1	33.3	9	23.1	10	23.8
<i>Amniotic fluid:</i>						
Polyhydramnios	2	66.7	19	48.7	21	50
Oligohydramnios	0	0	1	2.6	1	2.4
Short femur	0	0	4	10.3	4	9.5
Other anomalies	2	66.7	3	7.7	5	11.9

NT = nuchal translucency. JLS = jugular lymphatic sacs.

^a Witt et al. (1987), Benacerraf et al. (1989), Izquierdo et al. (1990), Sonesson et al. (1992), Nisbet et al. (1999), Achiron et al. (2000), Bradley et al. (2001), Menashe et al. (2002), Witters et al. (2002), Eccles et al. (2003), Gandhi et al. (2004), Ragavan and Vause (2005), Schluter et al. (2005), Becker et al. (2007), Bekker et al. (2007), Kiyota et al. (2008), Gonzalez-Huerta et al. (2010), Houweling et al. (2010).

^b (Malalignment) VSD (5), ASD (1), AVSD (1), AV canal (1), pericardial effusion (3), ventricular dysfunction (1), pulmonary stenosis (5), aortic stenosis (1), cardiomyopathy (6), supraventricular extrasystoles (1).

^c Pyelectasia; bilateral in most cases, in three cases unilateral.

abnormalities. We do not believe this strategy should be pursued, as it will not be cost-effective. More importantly, it will cause unnecessary anxiety in the majority of patients, given the fact that most fetuses with normal chromosomes and absence of structural anomalies will be absolutely fine at birth. Lee et al. suggest that the use of prenatal PTPN11 DNA testing based on selected ultrasonographic findings will identify Noonan syndrome in a significant proportion of fetuses. PTPN11 testing based on prenatal ultrasound abnormalities resulted in detection of a mutation in 16 and 2% of fetuses with cystic hygroma and increased NT, respectively (Lee et al., 2009). Based on our experience and on data from the literature we suggest that prenatal DNA testing is justified in case of increased NT, increased NF or cystic hygroma in the second trimester in combination with one or more of the characteristics mentioned in Table 2. Prenatal DNA testing can aid physicians in counseling parents, planning management options and in optimizing perinatal care. A PTPN11 gene mutation on chromosome 12 is found in about 50% of the cases (Tartaglia et al., 2001). In all other cases genetic investigation should be extended to mutations in other genes involved in the pathogenesis of Noonan syndrome, such as the SOS1, RAF1, KRAS and NRAS genes.

In case of prenatal features suggestive of Noonan syndrome, the parents should also be genetically examined, in view of the autosomal dominant inheritance (Van Huizen et al., 2005). Bearing in mind that the diagnosis of Noonan syndrome can be challenging in adult due to the high variability of the clinical characteristics and change in phenotype with age (Allanson, 1993).

In case of doubt, asking the parents for childhood pictures may reveal more pronounced Noonan syndrome features. Based on the presented cases we suggest that they may be even more pronounced prenatally. Therefore, use of 3D rendering of the fetal face in case of subtle anomalies after an increased NT and normal karyotype, can be a valuable tool in the prenatal assessment of these fetuses.

In conclusion, prenatal ultrasound findings in Noonan syndrome can be subtle and aspecific, but when above-mentioned characteristics are present (Table 1), additional targeted DNA analysis is indicated.

References

1. Achiron R., Heggesh J., Grisaru D. et al., 2000. Noonan syndrome: a cryptic condition in early gestation. *Am J Med Genet* 92(3): 159-165.
2. Allanson J. E., 1987. Noonan syndrome. *J Med Genet* 24(1): 9-13.
3. Allanson J. E., 1993. Noonan Syndrome. Gene Reviews [internet], Seattle (WA). University of Washington, Seattle; 1993-2001 Nov 15 [updated 2008 oct 07].
4. Becker K., Hughes H., Howard K. et al., 2007. Early fetal death associated with compound heterozygosity for Noonan syndrome-causative PTPN11 mutations. *Am J Med Genet A* 143A(11): 1249-1252.
5. Bekker M. N., Go A. T., Van Vugt J. M., 2007. Persistence of nuchal edema and distended jugular lymphatic sacs in Noonan syndrome. *Fetal Diagn Ther* 22(4): 245-248.
6. Benacerraf B. R., Greene M. F., Holmes L. B., 1989. The prenatal sonographic features of Noonan's syndrome. *J Ultrasound Med* 8(2): 59-63.
7. Bilardo C. M., Muller M. A., Pajkrt E., Clur S. A., Van Zalen M. M., Bijlsma E. K., 2007. Increased nuchal translucency thickness and

- normal karyotype: time for parental reassurance. *Ultrasound Obstet Gynecol* 30(1): 11-18.
8. Bradley E., Kean L., Twining P., James D., 2001. Persistent right umbilical vein in a fetus with Noonan's syndrome: a case report. *Ultrasound Obstet Gynecol* 17(1): 76-78.
 9. Brady A. F., Pandya P. P., Yuksel B., Greenough A., Patton M. A., Nicolaides K. H., 1998. Outcome of chromosomally normal livebirths with increased fetal nuchal translucency at 10-14 weeks' gestation. *J Med Genet* 35(3): 222-224.
 10. Eccles D., Meek D., Nwosu E. C., 2003. Noonan syndrome: diagnostic difficulties. A case report and literature review. *J Obstet Gynaecol* 23(6): 666-667.
 11. Gandhi S. V., Howarth E. S., Krarup K. C., Konje J. C., 2004. Noonan syndrome presenting with transient cystic hygroma. *J Obstet Gynaecol* 24(2): 183-184.
 12. Gonzalez-Huerta N. C., Valdes-Miranda J. M., Perez-Cabrera A., Pacheco-Cuellar G., Gonzalez-Huerta L. M., Cuevas-Covarrubias S. A., 2010. Noonan syndrome: prenatal diagnosis in a woman carrying a PTPN11 gene mutation. *J Matern Fetal Neonatal Med* 23(7): 688-691.
 13. Hiippala A., Eronen M., Taipale P., Salonen R., Hiilesmaa V., 2001. Fetal nuchal translucency and normal chromosomes: a long-term follow-up study. *Ultrasound Obstet Gynecol* 18(1): 18-22.
 14. Houweling A. C., De Mooij Y. M., Van der Burgt I., Yntema H. G., Lachmeijer A. M., Go A. T., 2010. Prenatal detection of Noonan syndrome by mutation analysis of the PTPN11 and the KRAS genes. *Prenat Diagn* 30(3): 284-286.
 15. Izquierdo L., Kushnir O., Sanchez D. et al., 1990. Prenatal diagnosis of Noonan's syndrome in a female infant with spontaneous resolution of cystic hygroma and hydrops. *West J Med* 152(4): 418-421.
 16. Jorge A. A., Malaquias A. C., Arnhold I. J., Mendonca B. B., 2009. Noonan syndrome and related disorders: a review of clinical features and mutations in genes of the RAS/ MAPK pathway. *Horm Res* 71(4): 185-193.
 17. Kiyota A., Tsukimori K., Yumoto Y. et al., 2008. Spontaneous resolution of cystic hygroma and hydrops in a fetus with Noonan's syndrome. *Fetal Diagn Ther* 24(4): 499-502.
 18. Lee K. A., Williams B., Roza K. et al., 2009. PTPN11 analysis for the prenatal diagnosis of Noonan syndrome in fetuses with abnormal ultrasound findings. *Clin Genet* 75(2): 190-194.
 19. Menashe M., Arbel R., Raveh D., Achiron R., Yagel S., 2002. Poor prenatal detection rate of cardiac anomalies in Noonan syndrome. *Ultrasound Obstet Gynecol* 19(1): 51-55.
 20. Nisbet D. L., Griffin D. R., Chitty L. S., 1999. Prenatal features of Noonan syndrome. *Prenat Diagn* 19(7): 642-647.
 21. Noonan J. A., 1994. Noonan syndrome. An update and review for the primary pediatrician. *Clin Pediatr (Phila)* 33(9): 548-555.
 22. Nora J. J., Nora A. H., Sinha A. K., Spangler R. D., Lubs H. A., 1974. The Ullrich-Noonan syndrome (Turner phenotype). *Am J Dis Child* 127(1): 48-55.
 23. Pajkrt E., Mol B. W., Bleker O. P., Bilardo C. M., 1999. Pregnancy outcome and nuchal translucency measurements in fetuses with a normal karyotype. *Prenat Diagn* 19(12): 1104-1108.
 24. Ragavan M., Vause S., 2005. Prenatal diagnosis of Noonan's syndrome: a case report. *J Obstet Gynaecol* 25(3): 305-306.
 25. Schluter G., Steckel M., Schiffmann H. et al., 2005. Prenatal DNA diagnosis of Noonan syndrome in a fetus with massive hygroma colli, pleural effusion and ascites. *Prenat Diagn* 25(7): 574-576.
 26. Schubbert S., Shannon K., Bollag G., 2007. Hyperactive Ras in developmental disorders and cancer. *Nat Rev Cancer* 7(4): 295-308.
 27. Senat M. V., Bussieres L., Couderc S. et al., 2007. Long-term outcome of children born after a first-trimester measurement of nu-

- chal translucency at the 99th percentile or greater with normal karyotype: a prospective study. *Am J Obstet Gynecol* 196(1): 53-56.
28. Sharland M., Burch M., McKenna W. M., Paton M. A., 1992. A clinical study of Noonan syndrome. *Arch Dis Child* 67(2): 178-183.
 29. Snijders R. J., Noble P., Sebire N., Souka A., Nicolaides K. H., 1998. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10-14 weeks of gestation. Fetal Medicine Foundation First Trimester Screening Group. *Lancet* 352(9125): 343-346.
 30. Sonesson S. E., Fouron J. C., Lessard M., 1992. Intrauterine diagnosis and evolution of a cardiomyopathy in a fetus with Noonan's syndrome. *Acta Paediatr* 81(4): 368-370.
 31. Souka A. P., Snijders R. J., Novakov A., Soares W., Nicolaides K. H., 1998. Defects and syndromes in chromosomally normal fetuses with increased nuchal translucency thickness at 10-14 weeks of gestation. *Ultrasound Obstet Gynecol* 11(6): 391-400.
 32. Souka A. P., Von Kaisenberg C. S., Hyett J. A., Sonek J. D., Nicolaides K. H., 2005. Increased nuchal translucency with normal karyotype. *Am J Obstet Gynecol* 192(4): 1005-1021.
 33. Tartaglia M., Mehler E. L., Goldberg R. et al., 2001. Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. *Nat Genet* 29(4): 465-468.
 34. Tartaglia M., Kalidas K., Shaw A. et al., 2002. PTPN11 mutations in Noonan syndrome: molecular spectrum, genotype-phenotype correlation, and phenotypic heterogeneity. *Am J Hum Genet* 70(6): 1555-1563.
 35. Van der Burgt I., 2007. Noonan syndrome. *Orphanet J Rare Dis* 2: 4.
 36. Van der Burgt I., Thoonen G., Roosenboom N. et al., 1999. Patterns of cognitive functioning in school-aged children with Noonan syndrome associated with variability in phenotypic expression. *J Pediatr* 135(6): 707-713.
 37. Van Huizen M. E., Pighetti M., Bijlsma E. K., Knecht A. C., Bilardo C. M., 2005. Increased nuchal translucency thickness: a marker for chromosomal and genetic disorders in both offspring and parents. *Ultrasound Obstet Gynecol* 26(7): 793-794.
 38. Witt D. R., Hoyme H. E., Zonana J. et al., 1987. Lymphedema in Noonan syndrome: clues to pathogenesis and prenatal diagnosis and review of the literature. *Am J Med Genet* 27(4): 841-856.
 39. Witters I., Spitz B., Van H. C., Devriendt K., Fryns J. P., Verbek K., 2002. Resolution of non-immune hydrops in Noonan syndrome with favorable outcome. *Am J Med Genet* 110(4): 408-409.

